Risk-Based Estimate of Human Fungal Disease Burden, China

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We conducted a systematic literature review to obtain risk population–based fungal disease incidence or prevalence data from China. Data were categorized by risk factors and extrapolated by using most recent demographic figures. A total of 71,316,101 cases (5.0% of the population) were attributed to 12 risk factors and 17 fungal diseases. Excluding recurrent *Candida* vaginitis (4,057/100,000 women) and onychomycosis (2,600/100,000 persons), aspergillosis (317/100,000 persons) was the most common problem; prevalence exceeded that in most other countries. Cryptococcal meningitis, an opportunistic infection, occurs in immunocompetent persons almost twice as often as AIDS. The pattern of fungal infections also varies geographically; *Talaromyces marneffei* is distributed mainly in the Pearl River Basin, and the Yangtze River bears the greatest histoplasmosis burden. New host populations, new endemic patterns, and high fungal burdens in China, which caused a huge impact on public health, underscore the urgent need for building diagnostic and therapeutic capacity.

Fungal diseases constitute a growing problem worldwide, causing a large, but poorly quantified, impact on public health (*1*). The incidence of fungal infections varies according to geographic region, socioeconomic conditions, and the number of persons with underlying conditions. China is one of the largest countries in the world (largest population and third largest land area). It has almost every type of weather niche, from the Pacific coast in the south to the snowy mountains in the Qinghai–Tibet Plateau, and even tropical rain forest. Many endemic fungal infections are present in China, along with globally distributed fungal pathogens. Although China has become the world's second largest economy, it is still a developing country, with millions of impoverished citizens who are susceptible to fungal infections. Fungal keratitis, one of the major causes of avoidable blindness, has been relatively neglected (*2*). Moreover, old pathogens such as *Histoplasma* and *Talaromyces marneffei* (talaromycosis) have expanded (*3,4*); new hosts contributing to new therapies for malignant and autoimmune disease have increased (*5,6*); and new patterns, including aspergillosis in pulmonary tuberculosis (PTB) and chronic obstructive pulmonary disease (COPD), are emerging (*7,8*). In addition, the lack of effective drugs, shortages of well-trained medical care personnel, and unaffordable antifungal drugs result in severe outcomes. Therefore, an estimation of fungal disease burden is needed for China to increase public health awareness and facilitate effective interventions.

As in most other countries, fungal infections are not reportable in China, and the incidence and prevalence are difficult to calculate because of the lack of population-based surveillance data and few high quality epidemiology studies. The Chinese National Fungal Diseases Surveillance System (http://www.chifungi.cn) was established on May 18, 2019, but no data have been released yet. Even with this dearth of data, we have attempted to estimate the burden of fungal disease in China.

Materials and Methods

Study Procedures

We conducted a literature review for published epidemiology papers that discussed fungal infections in China. If no epidemiological data existed for a particular fungal disease, we estimated the burden based on fungal infection incidence or prevalence and the specific populations at risk (Figure 1; Appendix Table 1, https://wwwnc.cdc.gov/EID/article/26/9/20-0016-App1.pdf).

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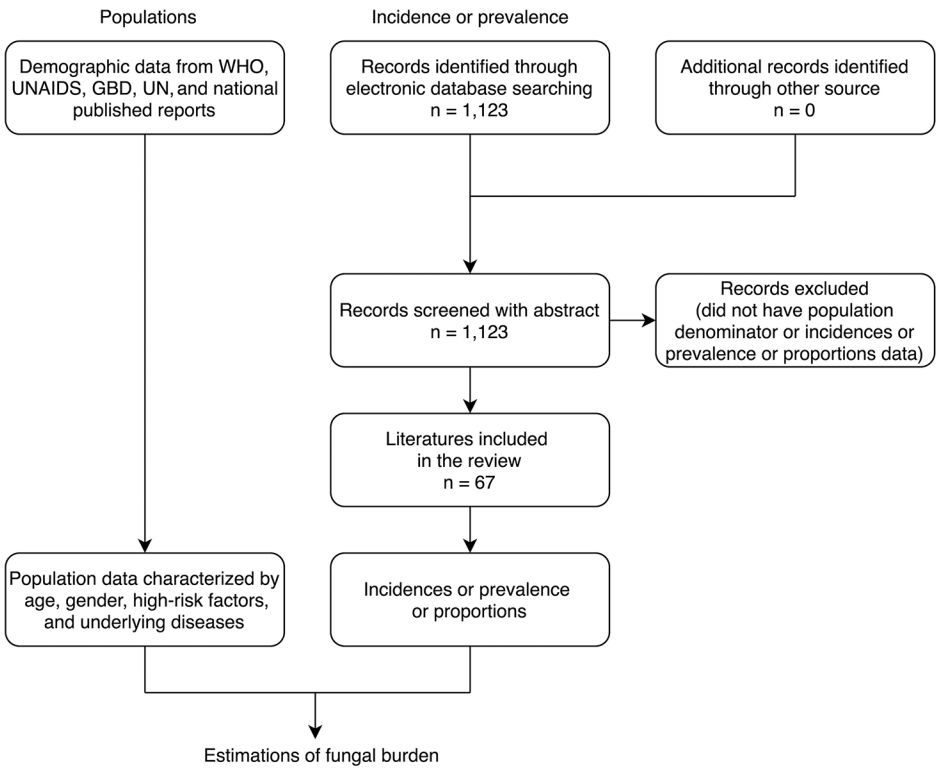

Figure 1. Flowchart of literature review for the human fungal disease burden in China. Reports published in English during January 1950–October 2019 were searched. GBD, Global Burden of Disease, Injuries, and Risk Factors Study; UNAIDS, the Joint Nations Program on HIV/AIDS; UN, United Nations Population Division; WHO, World Health Organization.

High-Risk Population Data

We obtained population statistics, including China's total, child, and female populations 14–49 years of age, from the United Nations Population Division (*9*). We derived data on HIV/AIDS in China from the Joint Nations Program on HIV/AIDS (UNAIDS) (*10*); we used the same source to calculate the proportion of HIV patients on antiretroviral therapy (ART). We consulted the World Health Organization (WHO) tuberculosis report to obtain data on tuberculosis patients; we assumed that 5.6% of these patients died (*11*). The numbers of lung cancer and hematological malignancy cases were derived from Global Cancer Observatory (GLOBOCAN) reports (*5*); data related to transplant recipients were derived from China Organ Transplantation Registration System (COTR) (*12*). For other high-risk populations, we extracted data from relevant published reports (Table 1).

Selection of Studies for Incidence or Prevalence Data

We conducted a systematic literature review and identified published epidemiology papers. We searched Web of Science, PubMed, and Embase databases for all the eligible studies published during January 1, 1950–October 7, 2019. Studies selected for this analysis were published in English; we included population-based incidence studies, population-based surveillance systems, and national investigation data. If no available incidence or prevalence data from China were found, we considered published global or international data. All search strings are listed in Appendix Table 2 and studies contributing to estimates for each fungal disease are listed in Appendix Table 3. All the assumptions and calculations for different fungal diseases are detailed in Table 2.

Analysis of Data

Candidiasis Burden Estimations

We estimated burdens of invasive candidiasis, *Candida* peritonitis, *Candida* peritonitis as a complication of chronic ambulatory peritoneal dialysis (CAPD), and recurrent vulvovaginal candidiasis (RVVC). To estimate invasive candidiasis, we first assessed candidemia incidence in intensive care units (ICUs). Because ≈20% of candidemia episodes in Asia occur in ICUs (*19*), we used these data to estimate annual incidence for all units. We then estimated *Candida* peritonitis by assuming that there were 2 episodes of candidemia per episode of intraabdominal candidiasis in the ICU, based on a large prospective study (*20*). In addition, we estimated *Candida* peritonitis in CAPD using data from the First Affiliated Teaching Hospital in Tianjin (*21*). For RVVC, when

Table 1. Population characteristics in China, by age, gender, high-risk factors, and underlying diseases*

Population characteristic	No., in thousands	Reference
Total population	1,433,784	UN, 2019 (*9*)
Population of children 0–14 y	254,930	UN, 2020 (*9*)
Female population, 15–49 y	403,377	UN, 2020 (*9*)
Population >40 y	688,074	UN, 2020 (*9*)
People living with HIV	810	UNAIDS, 2017 (*10*)
Proportion of HIV patients on ART	40%	UNAIDS, 2017 (*10*)
Adults living with HIV and CD4 <200 cells/μL	106	Assumes a 5-y decline in immunity
AIDS related deaths	26	UNAIDS, 2017 (*10*)
Annual cases of TB	856	WHO 2017 (*11*)
Annual cases of pulmonary TB who survive	844	WHO 2017 (*11*)
Adults with asthma (4.2%) population	49,512	Huang, 2019 (*13*)
Adults with COPD (7.2% of population)	102,377	Zhu, 2018 (*14*)
Adults with COPD admitted to hospital each year (20.1%)	29,382	Zhu, 2018 (*14*)
Lung cancer	774.3	GLOBOCAN, 2018 (*1*)
Liver transplants per year	4.73	COTR (*12*)
Renal transplants per year	10.8	COTR (*12*)
Lung transplants per year	0.3	COTR (*12*)
Heart transplants per year	0.56	COTR (*12*)
Allogeneic stem cell transplants per year	5.0	Xu, 2016 (*15*)
Acute myelogenous leukemia	41.2	40% of GLOBOCAN leukemia and multiple myeloma total, 2018 (*1*)
No. patients on peritoneal dialysis	73.9	Wilkie and Davies, 2017 (*16*)
Intensive care unit beds	86.0	Murthy, 2012 (*17*)
Intensive care admissions surviving >24 h	5,126	Du, 2013 (*18*)

*ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; COTR, China Organ Transplantation Registration System; TB, tuberculosis; UN, United Nations Population Division; UNAIDS, the Joint Nations Program on HIV/AIDS; WHO, World Health Organization.

prevalence data were not available, we used the rate of women with RVVC from a recent global estimate (*22*). We assumed that esophageal candidiasis occurred in 20% of patients with HIV who were not on ART and 5% of those taking ART annually (*23*). Oral candidiasis was estimated only in patients with HIV; we assumed that it occurs in 45% of patients with AIDS annually (*24*).

Aspergillosis Burden Estimations

We calculated burdens of invasive aspergillosis (IA), chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), and severe asthma with fungal sensitization (SAFS). We estimated the annual incidence of IA in hematological malignancy, solid and hematopoietic stem cell transplant (HSCT) recipients, lung cancer, COPD, and deaths from AIDS. We estimated that acute myeloid leukemia accounted for 40% of the annual incidence of all leukemias and multiple myeloma in 2018 (*5*). We took the rate of IA of 13% in hematological malignancy from a study from Taiwan (*25*), where mold-active prophylaxis was not given, and an equal number of cases were seen in all other leukemia and lymphoma cases. Among allogeneic HSCT recipients, we assumed an IA rate of 10% and rates in solid organ transplant recipients of 2% (renal), 6% (heart), 4% (liver), and 20% (lung) (*23*). For patients with lung cancer, we used a rate of 2.6% from a large study from China (*26*). To estimate the annual incidence of IA in patients with COPD, we used a recent study in Guangzhou Province, which found that the rate of IA in hospitalized patients with COPD was 3.9% (*27*). The annual hospitalization rate was a mean of 20.9%, and the number of patients with COPD came from a systematic review (*28*), from which we estimated the hospitalized patients with COPD. Although this information was not reported from China, we assumed a 4% autopsy incidence of IA in patients with AIDS (*29*).

We used the WHO 2017 figures for PTB to calculate CPA (*11*). We calculated CPA incidence after PTB based on our previous estimate, assuming that 22% of patients are left with a pulmonary cavity and that 22% of these patients develop CPA each year, as did 2% of those without a cavity (*30*). This calculation derives an annual incidence of CPA, which we converted to a 5-year period prevalence by assuming a 15% annual death or surgical resection rate. Given that PTB is one of several underlying causes of CPA, we conservatively assumed that PTB was primarily responsible for 33% of all CPA cases (*31*).

The reported rate of asthma in adults in China has increased from 1.42% in 2012 to 4.2% in 2019 (*13*). Ma et al. ascertained that 2.5% of these patients had ABPA (in secondary care) (*32*). Severe asthma proportion of adult asthmatics was estimated at 10%, as in other country estimates (*23*). We used a conservative fungal sensitization rate of 33% (as in other countries) to estimate the number of SAFS (*23*). No estimation

was made about cystic fibrosis in China because few patients currently survive to adulthood.

HIV-Related Infection Burden Estimation

We estimated burdens of cryptococcal meningitis (CM), *Pneumocystis* pneumonia (PCP), talaromycosis, and histoplasmosis. We ignored other HIV-related infections because of the lack of population-based data. We derived data for patients with AIDS from those who had a 5-year decline in CD4 counts to <200 cells/mL in the total population of HIV patients. We estimated the annual incidence of CM at 8% in patients with AIDS (CD4 count

Table 2. Assumptions and calculations for the estimations of fungal disease burden, China*

Fungal diseases†	Assumptions	Calculations
Candidemia	1. Candidemia episodes in ICU = (ICU beds × 365/median length of ICU stay) × (rate of candidemia in ICU/1,000 admissions) 2. 20% of candidemia episodes in Asia occur in ICU	Candidemia = Candidemia episodes in ICU/0.20
Candida peritonitis	Rate of *Candida* peritonitis is 50% of cases of candidemia in ICU	*Candida* peritonitis = candidemia in ICU × 50%
Candida peritonitis CAPD	1. 3.7% were *Candida* peritonitis in all episodes of infection 2. Overall infection incidence was 0.27 episodes/patient/year	*Candida* peritonitis CAPD = peritoneal dialysis × 0.27 × 3.7%
Oral candidiasis	Assumed to occur in 45% of AIDS cases annually	Oral candidiasis = AIDS × 45%
Esophageal candidiasis	Assumed to occur in 20% of HIV patients not on ART and 5% of patients taking ART annually	Esophageal candidiasis = (0.2 × HIV patients not on ART) + (0.05 × HIV patients on ART)
RVVC	Assumed to occur in 7.2% of the female population 15–49 years of age	RVVC = (female population 15–49) × 7.2%
IA	1. In hematologic malignancy, annual incidence of all leukemias and multiple myeloma × 40% × 13% a. Acute myeloid leukemia estimated at 40% of annual incidence of leukemias and multiple myeloma b. 13% of patients with acute myeloid leukemia developed IA 2. IA in solid and HSCT recipients: assumed 10% in a-HSCT recipients, 2% of renal transplants, 6% of heart transplants, 4% of liver transplants, 20% of lung transplants 3. IA in 2.6% of patients with lung cancer 4. IA in COPD: COPD patients × 20.9% × 3.9% a. Annual hospitalization rate for COPD = 20.9% b. 3.9% of hospitalized COPD patients developed IA 5. IA in 4% of HIV/AIDS patients	IA = IA in hematologic malignancy + IA in solid and HSCT recipients + IA in lung cancer patients + IA in COPD patients + IA in HIV/AIDS patients
CPA	1. TB-related CPA: assuming rate of 22% among patients with lung cavities, 2% of patients without cavities 2. 22% of patients with pulmonary TB have residual lung cavities 3. One third of underlying diseases of CPA are TB	Total CPA = TB-related CPA × 3
ABPA	1. 4.2% of adults in China have asthma 2. 2.5% of adults with asthma have ABPA	ABPA = adults with asthma × 2.5%
SAFS	1. Assume a conservative 33% rate of fungal sensitization in patients with severe asthma 2. 10% of adults with asthma have severe asthma	SAFS = adult population × 33% × 10%
CM	1. 7.1% of patients with HIV/AIDS 2. HIV-related CM is 21% of total CM 3. Annual incidence of 0.43/100,000 in children	CM = (7.1% × HIV/AIDS patients / 21%) + 0.43/100,000 × child population
PCP	1. 22.4% of HIV-positive patients during a 2y period 2. HIV-related PCP is 70.22% of total PCP	PCP = 22.4% × HIV/AIDS patients / 2 / 70.22%
Talaromycosis	Assume 20% of AIDS patients geographically exposed, attack rate 15%	Talaromycosis = HIV/AIDS patients × 20% × 15%
Histoplasmosis	Assume 67% of AIDS patients geographically exposed, attack rate 5%	Histoplasmosis = HIV/AIDS patients × 5% × 67%
Mucormycosis	Assume prevalence is 0.2/100,000 in total population	Mucormycosis = total population × 0.2/100,000
Fungal keratitis	0.007% of total population	Fungal keratitis = total population × 0.007%
Onychomycosis	2.6% of total population	Onychomycosis = total population × 2.6%

*ABPA, allergic bronchopulmonary aspergillosis; ART, antiretroviral therapy; CAPD, continuous ambulatory peritoneal dialysis; CM, cryptococcal meningitis; CPA, chronic pulmonary aspergillosis; HSCT, hematopoietic stem cell transplant: IA, invasive aspergillosis; ICU, intensive care unit; PCP, pneumocystis pneumonia; RVVC, recurrent *Candida* vaginitis; SAFS, severe asthma with fungal sensitization.

†Example for reading the table: burden of candidemia = candidemia episodes in ICU / 0.20 = (ICU beds × 365 / median length stay in ICU) × (rate of candidemia in ICU/1000 admissions) /0.20 = (86,027 × 365 / 6.126) × (3.2 / 1000) / 0.20 = 82,011.

<200 cells/mL) (*33*) and estimated the overall CM annual incidence based on the assumption that the proportion of HIV-positive patients with CM was 21% (*34*). In children, 23 cases of CM were diagnosed over a 5-year period (2007–2012) in Shijiazhuang, giving an annual incidence of 0.43/100,000 (*35*). We conservatively estimated the 2-year incidence of PCP at 22% of patients with AIDS (*36*), which comprises 70% of total cases (*37*). Only 20% of the HIV population was assumed to be geographically at risk for infection with *T. marneffei*; the attack rate was 15% in patients with AIDS (*3*). Disseminated histoplasmosis was assumed to occur in 5% of the geographically exposed population (estimated at 67%) of patients with AIDS (*4*).

Mucormycosis, Fungal Keratitis, and Onychomycosis Burden Estimation

Mucormycosis is a rare fungal infection; the prevalence rate is 0.2–140.0/1 million population (*38*). We used a global prevalence rate (2.0/1 million population) to estimate the burden. To estimate the burden of fungal keratitis, which is usually caused by *Fusarium* spp. and *Aspergillus* spp. in China, we used the overall prevalence of 0.007% according to a multicenter study (*2*). We used the global prevalence rate (2.6%) from 11 population-based studies to estimate the onychomycosis burden (*39*).

Epidemiology Maps

For talaromycosis and histoplasmosis, which showed new endemic trends, we prepared epidemiology maps according to the number of reported cases in China. We searched the PubMed database for articles published in China during January 1, 1950–October 7, 2019. Reports published in English were included. Search strings and references contributing to the talaromycosis map are listed in Appendix Table 4, and those contributing to the histoplasmosis map are listed in Appendix Table 5.

Prediction of HIV-Related Invasive Fungal Burden

We made a simple prediction model to estimate the HIV-related fungal burden by 2050. We derived the prediction data for total population in the next 50 years from UN data (*40*), and we collected data on HIV and AIDS cases during 2012–2017 to make a linear regression model to predict the number of HIV cases in 2050. If early testing and ART are at the current level, we estimate that 20.4% of HIV patients will develop advanced HIV disease over time (*10*). Based on our assumptions, we also predicted the burdens of invasive fungal diseases, including CM, PCP, and talaromycosis.

Results

Population Profiles

According to the UN data, the population of China was ≈1.4 billion in 2019, of whom 18% were children; 688 million adults were >40 years of age, of whom 403 million were women 15–49 years of age (*9*). The current total number of reported HIV infections in China is 810,000, and there were 26,000 AIDS-related deaths in 2017. Thus, 784,000 persons were living with HIV in China in 2019, of whom 60% were not receiving ART and 165,018 had AIDS (CD4 <200) (*10*). The detailed population characteristics and high-risk populations are described in Table 1.

Candidiasis Burden

The overall fungal burden in China, according to major risk factors, is summarized in Table 3. In 2012, there were an estimated 86,027 intensive care beds, in China and the rate of candidemia in ICU was documented at 3.2/1000 ICU admissions. The median length of stay in the ICU in China is 6.1 days. Thus, there are 16,402 candidemia episodes in the ICU, and we estimated a total of 82,011 episodes of candidemia per year in all units. Although *C. albicans* remains the most common species associated with candidiasis in ICU patients, other non–*albicans Candida* (NAC) is becoming increasingly common, and patients with NAC usually have longer antifungal therapy, longer ICU or hospital stay, and slightly higher death rates (*41*).

We also estimated 8,201 cases of postsurgical *Candida* peritonitis (intraabdominal candidiasis) by making the assumption that the rate of *Candida* peritonitis is 50% of cases of candidemia in the ICU. Given that there were 73,871 patients on CAPD in China in 2017, we estimated 738 peritonitis cases by using the *Candida* peritonitis episode rate of 0.01/patient-year.

Except for cutaneous disease, recurrent *Candida* vaginitis is the most common fungal disease, with aspergillosis, including IA, CPA, ABPA, and SAFS, next (Figure 2). We used the base case of RVVC prevalence in adult premenopausal women (15–49 years of age) previously published: 29,082,000 (range 21,812,000–36,353,000) affected women (*22*). In addition, 74,258 cases of oral candidiasis and 49,240 cases of esophageal candidiasis were expected annually in patients with HIV.

Aspergillosis Burden

We obtained an estimate of 1,178,747 cases of IA (82.1/100,000 population). We estimated 32,840 cases in immunocompromised patients and those

Table 3. Summary of fungal infection burden in China according to major risk factors*

Infection	No. infections per underlying disorder per year					Total no. cases	Rate/100,000 population
	None	HIV/AIDS	Respiratory	Cancer	ICU		
Candidemia	NE	NE	NE	65,609	16,402	82,011	5.72
Candida peritonitis							
ICU + surgery	NE	NE	NE	NE	8,939	8,939	0.62
CAPD	738	NE	NE	NE	NE	738	0.05
Oral candidiasis	NE	74,258	NE	NE	NE	74,258	5.18
Esophageal candidiasis	NE	49,204	NE	NE	NE	49,204	3.43
Recurrent *Candida* vaginitis	29,082,000	NE	NE	NE	NE	29,082,000	4,056.68†
IA	NE	1,040	1,145,908	31,800	NE	1,178,748	82.21
CPA	NE	NE	488,716	NE	NE	488,716	34.09
ABPA	NE	NE	1,237,797	NE	NE	1,237,797	86.33
SAFS	NE	NE	1,633,892	NE	NE	1,633,892	113.96
CM	26,249	13,086	NE	26,172	NE	65,607	4.57
PCP	NE	18,482	NE	9,241	NE	27,723	1.93
Talaromycosis	NE	4,951	NE	NE	NE	4,951	0.35
Mucormycosis	2,868	NE	NE	NE	NE	2,868	0.20
Fungal keratitis	100,365	NE	NE	NE	NE	100,365	7.00
Onychomycosis	37,278,384	NE	NE	NE	NE	37,278,384	2,600.00
Total burden	66,490,604	161,021	4,506,313	132,822	25,341	71,316,101	7,002.32

*ABPA, allergic bronchopulmonary aspergillosis; ART, antiretroviral therapy; CAPD, continuous ambulatory peritoneal dialysis; CM, cryptococcal meningitis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; ICU, intensive care unit; NE, no estimation could be made because of the lack of data; PCP, pneumocystis pneumonia; SAFS, severe asthma with fungal sensitization.
†Female population only.

with cancer; of these, 20,000 were in patients with lung cancer and 1,040 in patients with AIDS. The remainder of IA cases in this immunocompromised group were in patients with hematologic malignancies, lymphoma, and transplants. We also calculated 1,145,908 IA cases derived from COPD.

In China, there were 844,500 survivors of tuberculosis in 2017 (*11*). We expect an annual incidence of 51,683 cases of tuberculosis-related CPA, and we estimated a 5-year period prevalence of 162,905 cases. Because tuberculosis probably comprises only one third of underlying CPA, the total period prevalence estimate is 488,716 cases (34/100,000 population).

Nearly 50 million adults with asthma live in China; of these, 10% have severe asthma. Regarding ABPA, the assumption is that 2.5% of adult asthmatics are affected, leading to a prevalence of 1,237,797 cases. Among patients with severe asthma, we estimate that 1.6 million have SAFS.

Burdens of HIV-Related Infections

CM occurs mainly in immunocompromised populations other than HIV patients in China, as well as in immunocompetent individuals. We thus obtained an estimate of adult CM: 13,086 in patients with AIDS and 26,172 each in immunocompromised and in immunocompetent persons. For CM in children, we estimated 77 cases annually, with an annual incidence of 0.43/100,000 population. We calculated a total of 65,507 CM cases.

We estimated the number of patients with PCP in China as 27,723 (18,482 with HIV and 9,241 with other immunocompromised conditions). This estimate implies an annual incidence of 1.93/100,000 population.

We estimated 4,951 talaromycosis cases in patients with AIDS in southern China. From the literature review, we identified 3,163 cases from 12 different provinces. The provinces with the highest prevalence are Guangxi and Guangdong, which each reported >1,000 cases (Figure 3, panel A). Both provinces are located in Pearl River Basin, possibly indicating an endemic trend.

We identified 380 histoplasmosis cases in China from the literature review (Figure 3, panel B). Most of the cases were reported in the region where the Yangtze River flows, also suggesting a new endemic pattern in China. Disseminated histoplasmosis in patients with AIDS was assumed to affect 5,528 persons annually, but we were unable to estimate the burden in non–HIV-infected persons or the burden of chronic pulmonary histoplasmosis. For the prediction of HIV-related invasive fungal burden by 2050, using annual data from 2012–2017 and extrapolating with our estimates, we expect 86,303 cases of PCP, 61,105 cases of CM, and 23,117 cases of *T. marneffei* infection (Figure 4).

Mucormycosis, Fungal Keratitis, and Onychomycosis Burden

We estimated mucormycosis using the global prevalence rate and calculated 2,868 cases. We estimated fungal keratitis based on the total population and estimated 100,365 cases of fungal keratitis annually in China. We estimated 37,278,384 cases of onychomycosis using the global data.

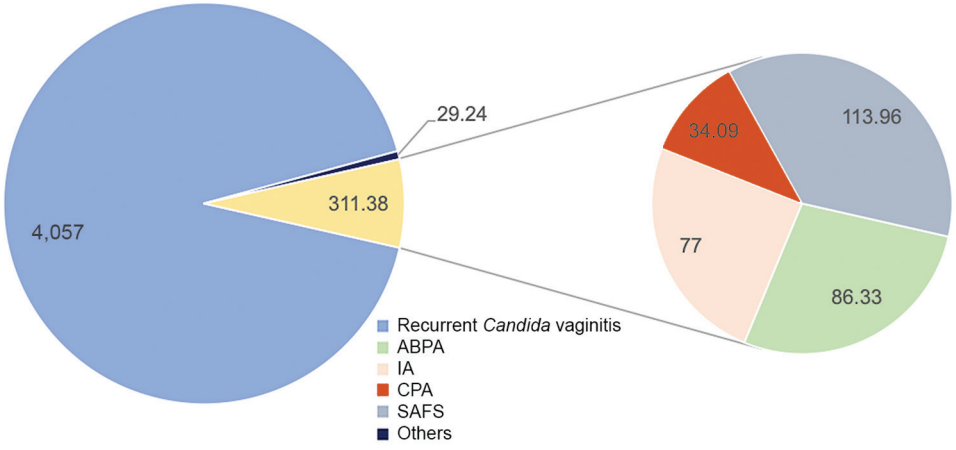

Figure 2. Estimated annual incidence (cases/100,000 population) of common fungal diseases in China. ABPA, allergic bronchopulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; SAFS, severe asthma with fungal sensitization.

Discussion

In this study, we estimated that 71 million persons suffer from a fungal disease in China. A total of 2.4% of the population is affected (excluding onychomycosis because it is superficial), similar to results in other reports from Senegal, Brazil, France, Korea and Germany; the prevalence range is 1.6%–3.6% (*1*). Multiple new host risk factors other than HIV/AIDS or hematologic malignancy, especially COPD, asthma, and lung cancer, are associated with fungal disease. We found that even immunocompetent children and women may develop fungal diseases. Chronic respiratory diseases, notably PTB and COPD, are risk factors for all manifestations of aspergillosis. Old pathogens, including *T. marneffei* and *Histoplasma capsulatum*, exhibit new endemic trends; the Pearl River Basin bears the greatest burden for *T. marneffei* and the Yangtze River for *H. capsulatum*. Our study contributes to the currently limited data on the burden of fungal disease in China and provides a basis for public health and research priorities.

The incidence of candidiasis has increased in recent years (*17*). Candidemia is probably underestimated, as we have used only ICU data to explore the total burden of all high-risk populations. Considering the wide use of broad-spectrum antimicrobial drugs and the demographic shift with a largely increasing elderly population, we expect infections to be on the rise.

We have estimated the oral and esophageal candidiasis burdens in HIV-positive patients; these are certainly underestimates of these infections, because many of the populations at risk could not be assessed, such as patients with cancer, those taking oral or inhaled corticosteroids, and newborns. Although the proportions of oral or esophageal candidiasis in this kind of population might be small, given the relatively large size compared to the rather small HIV population, these cases could multiply our estimates. In addition, oral and esophageal candidiasis and colonization are associated with mucosal malignancy and particularly associated with high alcohol consumption (*42*). If the high number of unsuspected cases of esophageal candidiasis based on data from South Korea is also true in China, this association could contribute to the high number of esophageal cancers seen annually in China (307,359 cases) (*43*), which could further increase the social and economic burden.

IA is usually severe and fatal, unless diagnosed early. Although profoundly immunocompromised patients are at higher risk, the enormous estimate for China is mostly driven by COPD (97%). Our estimate of IA prevalence in liver transplant recipients of 4% is higher than the report from China at 1.7% (*44*), but that study was based on histology or culture alone, which is much less sensitive than *Aspergillus* antigen detection. The same applies to renal transplant recipients (*45*). Other underlying conditions were newly recognized risk factors for IA, such as diabetes mellitus, systemic lupus erythematosus, and postoperative and burn infections related to contaminated air in hospitals; these were not included in our estimation because of the unavailable incidence rate. Nevertheless, the number of IA cases could also be overestimated because *Aspergilli* are common fungi in the environment, and a positive result from non–aseptic fluid culture does not always represent disease. On the other hand, we have not estimated IA in most medical ICU patients, and not included the potential for IA complicating annual influenza cases or an epidemic.

In contrast to other countries, where CM is often diagnosed in patients with HIV or immunocompromised patients, in China, a high proportion of cryptococcosis was reported in immunocompetent persons (*34*). Jiang et al. reported on 159 HIV-negative

patients with CM, of whom 85 were normal hosts; however, whether these persons were immunocompetent is unknown, because several genetic predisposition factors for CM have been found in the ethnic Chinese population (*46*). Most large-scale studies have been conducted in adults; few were dedicated to pediatric populations. Although children account for only 0.9%–2.0% of all cryptococcal cases, the death rate is high, up to 43% (*47*). In a 12-year retrospective study in Beijing, 53 pediatric case-patients were encountered, of whom 41 had no underlying conditions (*48*). However, the denominator was unavailable. Only an annual incidence of 0.43/100,000 HIV-negative children was reported from the Acute Meningitis-Encephalitis Syndrome Surveillance project (*35*). Because of the lack of surveillance networks in China, additional studies are required, especially for immunocompetent patients.

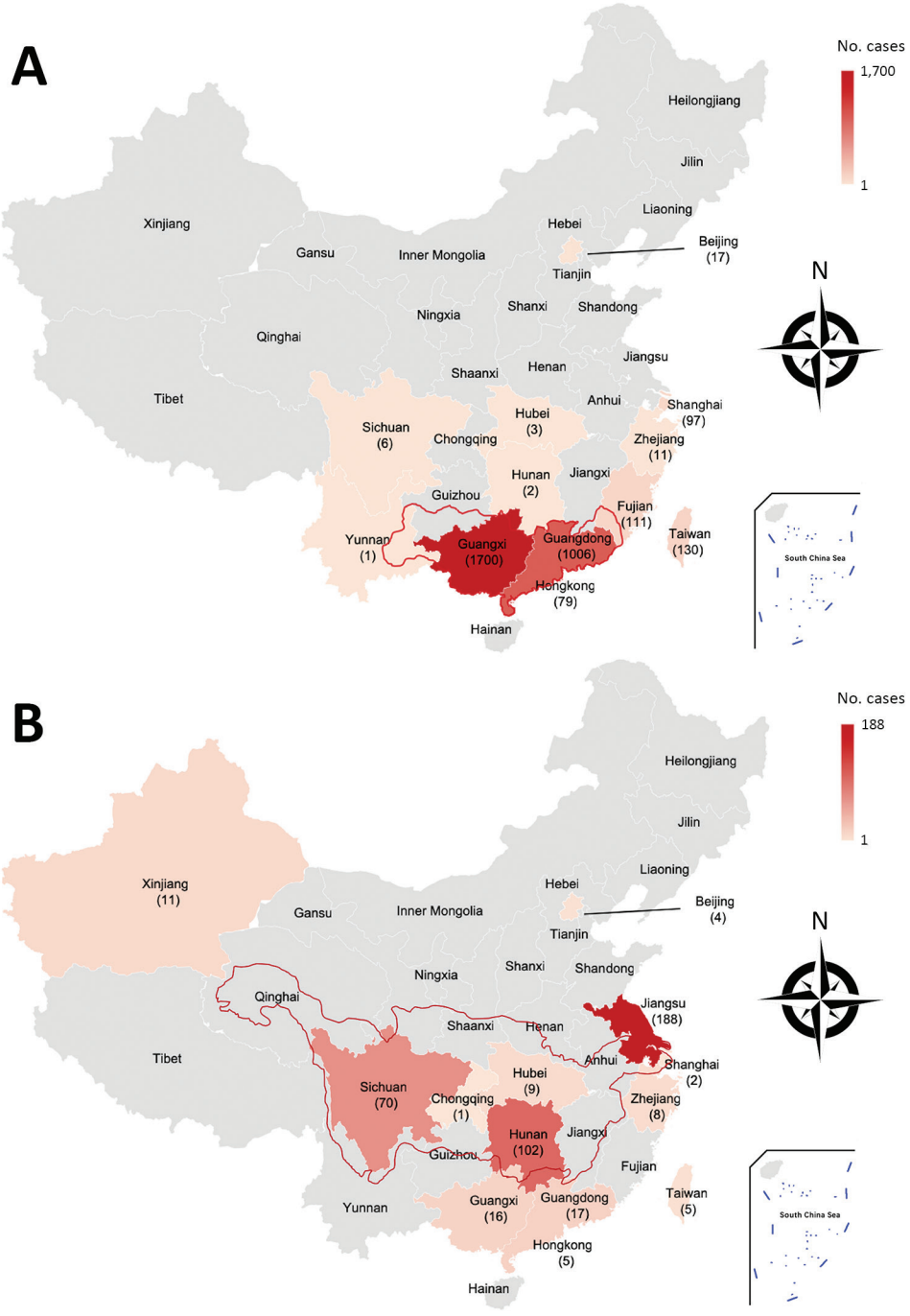

Figure 3. Epidemiology maps for talaromycosis and histoplasmosis, according to the number of reported cases, China. A) Map for talaromycosis. Red border indicates Pearl River basin. B) Map for histoplasmosis. Red border indicates Yangtze River region. Reports published in English during January 1950–October 2019 were searched.

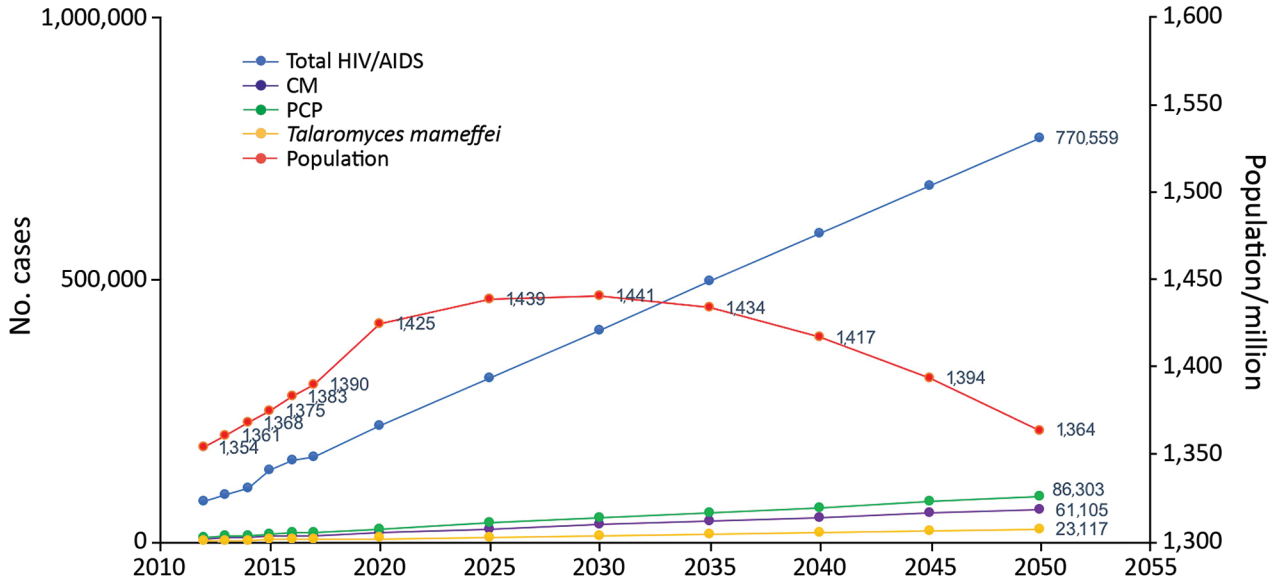

Figure 4. Prediction of HIV-related invasive fungal burden in China by 2050, based on ART and HIV-related disease incidence levels for 2012–2017. ART, antiretroviral therapy; CM, cryptococcal meningitis; PCP, pneumocystis pneumonia.

Although histoplasmosis is a common endemic mycosis in North America, several sporadic cases were reported in China, especially in the Yangtze River region, which was traditionally thought to be nonendemic for *Histoplasma capsulatum* (*3*). However, >300 histoplasmosis cases have been reported since 1990, and only 17 were identified as imported cases, indicating many authochthonous cases in China (*3*). *T. marneffei* infection, the other fatal endemic opportunistic fungal infection disease in Asia, was reported mostly in the southern part of China, possibly linked to an altered microeukaryotic community in subtropical rivers caused by global warming (*49*). Because this disease was associated mainly with HIV/AIDS, we estimated the incidence only in HIV-positive patients. In addition, given the low national reported statistics of HIV infection (*3*), the estimation of talaromycosis burden may be far underestimated. More large population-based studies are needed to better clarify the frequency of these fungal infections in these at-risk patients.

The government of China has worked to improve healthcare over the past 2 decades. However, HIV remains a major public health issue, showing the fastest growth among 45 infectious diseases during 2004–2013 with an annual percentage change of 16.3% (*50*). Therefore, we made a prediction of HIV-related opportunistic fungal infections. According to our data, it is likely that CM, PCP, and *T. marneffei* infection are major health burdens, which call for much more clinical training, financial support, and public policies.

Even though the incidence rate was low compared with those for bacterial and viral infections, our study represents a heavy fungal burden considering the immense population base and high mortality of nonsuperficial mycoses. The drawbacks of our study are the few studies conducted in the country for some infections; the prevalence or incidence are not available for those diseases, including sporotrichosis and some dermatophytosis. Epidemiologic studies are required and population-based surveillance data remain to be estimated, both nationally and regionally. Improved epidemiologic data are necessary for better awareness, better diagnostics, and better therapies.

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About the Author

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References

1. Global Action Fund for Fungal Infections. Publications: key recent contributions to the academic literature and individual country burdens [cited 2019 Oct 7]. http://www.gaffi.org/media/academic-papers
2. Song X, Xie L, Tan X, Wang Z, Yang Y, Yuan Y, et al. A multi-center, cross-sectional study on the burden of infectious keratitis in China. PLoS One. 2014;9:e113843. https://doi.org/10.1371/journal.pone.0113843
3. Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffei* infection: an emerging disease in mainland China. Mycopathologia. 2013;175:57–67. https://doi.org/10.1007/s11046-012-9577-0
4. Pan B, Chen M, Pan W, Liao W. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. Mycoses. 2013;56:212–21. https://doi.org/10.1111/myc.12029
5. The Lancet. GLOBOCAN 2018: counting the toll of cancer. Lancet. 2018;392:985. https://doi.org/10.1016/S0140-6736(18)32252-9
6. Hung ML, Liao HT, Chen WS, Chen MH, Lai CC, Tsai CY, et al. Invasive aspergillosis in patients with systemic lupus erythematosus: a retrospective study on clinical characteristics and risk factors for mortality. Lupus. 2018;27:1944–52. https://doi.org/10.1177/0961203318796294
7. Chinese State Statistical Bureau. China Statistical Yearbook 2018 [cited 2019 Oct 7]. http://www.stats.gov.cn/tjsj/ndsj/2018/indexch.htm
8. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, et al.; China Pulmonary Health Study Group. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet. 2018;391:1706–17. https://doi.org/10.1016/S0140-6736(18)30841-9
9. United Nations Population Division. World population prospects 2019 [cited 2019 Oct 7]. https://population.un.org/wpp/Download/Standard/Population
10. UNAIDS. AIDS info: people living with AIDS receiving ART [cited 2019 Oct 7]. http://www.unaids.org/en/dataanalysis/datatools/aidsinfo
11. World Health Organization. Tuberculosis country profiles [cited 2019 Oct 7]. http://www.who.int/tb/country/data/profiles/en/index.html
12. Chinese Ministry of Health. China Organ Transplantation Registration System [cited 2019 Oct 7]. http://www.cotr.cn
13. Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al.; China Pulmonary Health (CPH) Study Group. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394:407–18. https://doi.org/10.1016/S0140-6736(19)31147-X
14. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:1353–64. https://doi.org/10.2147/COPD.S161555
15. Xu LP, Wu DP, Han MZ, Huang H, Liu QF, Liu DH, et al. A review of hematopoietic cell transplantation in China: data and trends during 2008–2016. Bone Marrow Transplant. 2017;52:1512–8. https://doi.org/10.1038/bmt.2017.59
16. Wilkie M, Davies S. Insights on peritoneal dialysis in China. Perit Dial Int. 2018;38(Suppl 2):S16–8. https://doi.org/10.3747/pdi.2018.00224
17. Murthy S, Wunsch H. Clinical review: international comparisons in critical care—lessons learned. Crit Care. 2012;16:218. https://doi.org/10.1186/cc11140
18. Du B, An Y, Kang Y, Yu X, Zhao M, Ma X, et al.; China Critical Care Clinical Trial Group. Characteristics of critically ill patients in ICUs in mainland China. Crit Care Med. 2013;41:84–92. https://doi.org/10.1097/CCM.0b013e31826a4082
19. Tan BH, Chakrabarti A, Li RY, Patel AK, Watcharananan SP, Liu Z, et al.; Asia Fungal Working Group (AFWG). Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. Clin Microbiol Infect. 2015;21:946–53. https://doi.org/10.1016/j.cmi.2015.06.010
20. Montravers P, Mira J-P, Gangneux J-P, Leroy O, Lortholary O; AmarCand study group. A multicentre study of a ntifungal strategies and outcome of *Candida* spp. peritonitis in intensive-care units. Clin Microbiol Infect. 2011;17:1061–7. https://doi.org/10.1111/j.1469-0691.2010.03360.x
21. Hu S, Tong R, Bo Y, Ming P, Yang H. Fungal peritonitis dialysis: 5-year review from a North China center. Infection. 2019;47:35–43. https://doi.org/10.1007/s15010-018-1204-7
22. Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R. Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect Dis. 2018;18:e339–47. https://doi.org/10.1016/S1473-3099(18)30103-8
23. Gamaletsou MN, Drogari-Apiranthitou M, Denning DW, Sipsas NV. An estimate of the burden of serious fungal diseases in Greece. Eur J Clin Microbiol Infect Dis. 2016;35:1115–20. https://doi.org/10.1007/s10096-016-2642-8
24. Matee MI, Scheutz F, Moshy J. Occurrence of oral lesions in relation to clinical and immunological status among HIV-infected adult Tanzanians. Oral Dis. 2000;6:106–11. https://doi.org/10.1111/j.1601-0825.2000.tb00110.x
25. Chen CY, Sheng WH, Tien FM, Lee PC, Huang SY, Tang JL, et al. Clinical characteristics and treatment outcomes of pulmonary invasive fungal infection among adult patients with hematological malignancy in a medical centre in Taiwan, 2008–2013. J Microbiol Immunol Infect. 2020;53:106–14. https://doi.org/10.1016/j.jmii.2018.01.002
26. Yan X, Li M, Jiang M, Zou LQ, Luo F, Jiang Y. Clinical characteristics of 45 patients with invasive pulmonary aspergillosis: retrospective analysis of 1711 lung cancer cases. Cancer. 2009;115:5018–25. https://doi.org/10.1002/cncr.24559
27. Xu H, Li L, Huang WJ, Wang LX, Li WF, Yuan WF. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China. Clin Microbiol Infect. 2012;18:403–8. https://doi.org/10.1111/j.1469-0691.2011.03503.x
28. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:1353–64. https://doi.org/10.2147/COPD.S161555
29. Khoo S, Denning DW. Invasive aspergillosis in patients with AIDS. Clin Infect Dis. 1994;19(suppl1):S41–8. https://doi.org/10.1093/clinids/19.supplement_1.s41
30. Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ. 2011;89:864–72. https://doi.org/10.2471/BLT.11.089441
31. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J. 2011;37:865–72. https://doi.org/10.1183/09031936.00054810
32. Ma YL, Zhang WB, Yu B, Chen YW, Mu S, Cui YL. Prevalence of allergic bronchopulmonary aspergillosis in Chinese patients with bronchial asthma [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi. 2011;34:909–13.
33. Chen J, Zhang R, Shen Y, Liu L, Qi T, Wang Z, et al. Serum cryptococcal antigen titre as a diagnostic tool and a predictor of mortality in HIV-infected patients with cryptococcal

meningitis. HIV Med. 2019;20:69–73. https://doi.org/10.1111/hiv.12679
34. Li Z, Liu Y, Cao H, Huang S, Long M. Epidemiology and clinical characteristics of cryptococcal meningitis in China (1981–2013): a review of the literature. Med Mycol: Open Access. 2017;3:1. https://doi.org/10.21767/2471-8521.100022
35. Guo J, Zhou J, Zhang S, Zhang X, Li J, Sun Y, et al. A case-control study of risk factors for HIV-negative children with cryptococcal meningitis in Shi Jiazhuang, China. BMC Infect Dis. 2012;12:376. https://doi.org/10.1186/1471-2334-12-376
36. Chan CK, Alvarez Bognar F, Wong KH, Leung CC, Tam CM, Chan KC, et al. The epidemiology and clinical manifestations of human immunodeficiency virus-associated tuberculosis in Hong Kong. Hong Kong Med J. 2010;16:192–8.
37. Guo F, Chen Y, Yang SL, Xia H, Li XW, Tong ZH. Pneumocystis pneumonia in HIV-infected and immunocompromised non-HIV infected patients: a retrospective study of two centers in China. PLoS One. 2014;9:e101943. https://doi.org/ 10.1371/journal.pone.0101943
38. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel). 2019;5:26. https://doi.org/10.3390/jof5010026
39. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. J Eur Acad Dermatol Venereol. 2014;28:1480–91. https://doi.org/10.1111/jdv.12323
40. United Nations Population Division. Demographic components of future population growth [cited 2019 Oct 7]. https://www.un.org/en/development/desa/population/theme/trends/dem-comp-change.asp
41. Gong X, Luan T, Wu X, Li G, Qiu H, Kang Y, et al. Invasive candidiasis in intensive care units in China: risk factors and prognoses of *Candida albicans* and non-*albicans Candida* infections. Am J Infect Control. 2016;44:e59–63. https://doi.org/10.1016/j.ajic.2015.11.028
42. Alnuaimi AD, Wiesenfeld D, O'Brien-Simpson NM, Reynolds EC, McCullough MJ. Oral *Candida* colonization in oral cancer patients and its relationship with traditional risk factors of oral cancer: a matched case-control study. Oral Oncol. 2015;51:139–45. https://doi.org/10.1016/j.oraloncology.2014.11.008
43. Choi JH, Lee CG, Lim YJ, Kang HW, Lim CY, Choi JS. Prevalence and risk factors of esophageal candidiasis in healthy individuals: a single center experience in Korea. Yonsei Med J. 2013;54:160–5. https://doi.org/10.3349/ymj.2013.54.1.160
44. Yang CH, He XS, Chen J, Ouyang B, Zhu XF, Chen MY, et al. Fungal infection in patients after liver transplantation in years 2003 to 2012. Ann Transplant. 2012;17:59–63. https://doi.org/10.12659/AOT.883695
45. Zhang XD, Hu XP, Yin H, Wang W, Zhang X, Ma LL, et al. *Aspergillus* pneumonia in renal transplant recipients. Chin Med J (Engl). 2008;121:791–4. https://doi.org/10.1097/00029330-200805010-00007
46. Jiang YK, Wu JQ, Zhao HZ, Wang X, Wang RY, Zhou LH, et al. Genetic influence of Toll-like receptors on non-HIV cryptococcal meningitis: an observational cohort study. EBioMedicine. 2018;37:401–9. https://doi.org/10.1016/j.ebiom.2018.10.045
47. Gumbo T, Kadzirange G, Mielke J, Gangaidzo IT, Hakim JG. *Cryptococcus neoformans* meningoencephalitis in African children with acquired immunodeficiency syndrome. Pediatr Infect Dis J. 2002;21:54–6. https://doi.org/ 10.1097/00006454-200201000-00012
48. Liu L, Guo L, Liu Y, Chen T, Li S, Yang Y, et al. Clinical characteristics and prognosis of pediatric cryptococcosis in Beijing Children's Hospital, 2002–2014. Eur J Pediatr. 2017;176:1235–44. https://doi.org/10.1007/s00431-017-2974-0
49. Chen W, Ren K, Isabwe A, Chen H, Liu M, Yang J. Stochastic processes shape microeukaryotic community assembly in a subtropical river across wet and dry seasons. Microbiome. 2019;7:138. https://doi.org/10.1186/s40168-019-0749-8
50. Yang S, Wu J, Ding C, Cui Y, Zhou Y, Li Y, et al. Epidemiological features of and changes in incidence of infectious diseases in China in the first decade after the SARS outbreak: an observational trend study. Lancet Infect Dis. 2017;17:716–25. https://doi.org/10.1016/S1473-3099(17)30227-X

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Risk-Based Estimate of Human Fungal Disease Burden, China

Appendix

Appendix Table 1. Definitions of fungal diseases*

Fungal disease	Definition
Candidiasis	
Candidemia	Presence in the blood of fungi of the genus *Candida*
Candida peritonitis	Intraabdominal infection with *Candida* spp., often with coexisting bacterial infection, involving the peritoneum in most cases
Candida peritonitis (CAPD)	*Candida* peritonitis occurring during continuous ambulatory peritoneal dialysis
Oral candidiasis	Oral mucosa infection caused by *Candida* spp.
Esophageal candidiasis	Esophageal mucosa infection caused by *Candida* spp.
Recurrent *Candida* vaginitis (RVVC)	Four or more episodes of symptomatic vulvovaginal candidiasis within 1 year, at least some of which are mycologically confirmed
Aspergillosis	
IA	A rapidly progressive, often fatal infection caused by *Aspergillus* spp that occurs in patients who are immunosuppressed (e.g., leukemia) or critically ill (e.g., severe influenza)
CPA	A long-term *Aspergillus* infection (>3 months) of the lung; includes several disease manifestations, including aspergilloma, *Aspergillus* nodules, chronic cavitary pulmonary aspergillosis, and chronic fibrosing pulmonary aspergillosis
ABPA	A hypersensitivity reaction to *Aspergillus* species (generally *A. fumigatus*) that occurs almost exclusively in patients with asthma or, less commonly, cystic fibrosis
SAFS	Asthma with refractory symptoms, sensitization to ≥1 common fungi, but lacking diagnostic criteria for ABPA (such as *Aspergillus*-specific IgG)
HIV-related fungal diseases	
CM	A type of meningitis caused by *Cryptococcus*
PCP	A serious infection caused by the fungus *Pneumocystis jirovecii*, in both HIV-infected and other immunocompromised patients
Endemic fungal diseases	
Talaromyces marneffei infection	Talaromycosis is an invasive fungal infection, usually found in HIV-infected persons, caused by the dimorphic fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*), which is endemic in Southeast Asia (in northern Thailand, Vietnam, and Myanmar), East Asia (in southern China, Hong Kong, and Taiwan), and South Asia (in northeastern India)

Fungal disease	Definition
Histoplasmosis	Histoplasmosis is caused by a fungus called *Histoplasma*. This fungus grows mainly in the central, southeastern, and mid-Atlantic United States and South Asia. The AIDS pandemic has elucidated a worldwide risk for histoplasmosis, including areas previously unknown to be endemic. In this article, only disseminated histoplasmosis is estimated.
Mucormycosis	A serious but rare fungal infection caused by a group of molds called Mucormycetes. Mucormycosis affects mainly diabetic or immunocompromised patients, occasionally others after trauma or intravenous drug abuse
Fungal keratitis	An infection of the cornea caused by a fungus
Onychomycosis	Fungal infection of the toenails or fingernails that may involve any component of the nail unit, including the matrix, bed, or plate, caused by many different fungi, including dermatophytes

* ABPA, allergic bronchopulmonary aspergillosis; CAPD, continuous ambulatory peritoneal dialysis; CM, cryptococcal meningitis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; PCP, pneumocystis pneumonia; SAFS, severe asthma with fungal sensitization. Global prevalence was used to estimate RVVC, mucormycosis, and onychomycosis cases. When the Chinese or global prevalence or incidence were not available, burdens of some fungal diseases were not estimated, including endemic fungal infections like sporotrichosis and coccidioidomycosis and some dermatophytosis (tinea corporis, tinea capitis, tinea pedis, tinea cruris).

Appendix Table 2. Literature search results for fungal diseases*

Fungal disease	Search string	No. studies identified
Candidemia	(candidemia OR candidaemia) AND (incidence OR prevalence) AND China	60
Candida peritonitis	(*candida* peritonitis) AND (incidence OR prevalence) AND China	10
Candida peritonitis (CAPD)	(continuous ambulatory peritoneal dialysis OR CAPD) AND (*candida* peritonitis) AND (incidence OR prevalence) AND China	5
Oral candidiasis	(oral candidiasis) AND (incidence OR prevalence) AND China	76
Esophageal candidiasis	(oesophageal candidiasis OR esophageal candidiasis) AND (incidence OR prevalence) AND China	7
Recurrent *Candida* vaginitis	(recurrent candida vaginitis OR RVVC) AND (incidence OR prevalence) AND China	6
IA	(invasive aspergillosis) AND (incidence OR prevalence) AND China	89
CPA	(chronic pulmonary aspergillosis OR CPA) AND (incidence OR prevalence) AND China	79
ABPA	(allergic bronchopulmonary aspergillosis OR ABPA) AND (incidence OR prevalence) AND China	11
SAFS	(asthma with fungal sensitization OR SAFS) AND (incidence OR prevalence) AND China	10
CM	(cryptococcal meningitis) AND (incidence OR prevalence) AND China	47
PCP	(pneumocystis pneumonia OR pneumocystis jirovecii pneumonia OR PCP OR PJP) AND (incidence OR prevalence) AND China)	110
Talaromyces marneffei infection	(*Talaromyces marneffei* OR *Ienicillium marneffei* OR talaromycosis) AND (incidence OR prevalence) AND China	59
Histoplasmosis	(*histoplasma capsulatum* OR histoplasmosis) AND (incidence OR prevalence) AND China	23
Mucormycosis	(mucormycosis OR zygomycosis OR *mucorales*) AND (incidence OR prevalence); filters: meta-analysis, review, systematic reviews	270
Fungal keratitis	(fungal keratitis) AND (incidence OR prevalence) AND China	64
Onychomycosis	Onychomycosis AND (incidence OR prevalence); filters: meta-analysis, review, systematic reviews	197

*Reports published in English during January 1950–October 2019 were searched. ABPA, allergic bronchopulmonary aspergillosis; CAPD, continuous ambulatory peritoneal dialysis; CM, cryptococcal meningitis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; PCP, pneumocystis pneumonia; PJP, pneumocystis jirovecii pneumonia; RVVC, recurrent *Candida* vaginitis; SAFS, severe asthma with fungal sensitization.

Appendix Table 3. Studies contributing to estimates of incidence or prevalence of fungal diseases in China*

Invasive aspergillosis
GLOBOCAN 2018: counting the toll of cancer. The Lancet. 2018;392:985.
Chen CY, Sheng WH, Tien FM, Lee PC, Huang SY, Tang JL, et al. Clinical characteristics and treatment outcomes of pulmonary invasive fungal infection among adult patients with hematological malignancy in a medical centre in Taiwan, 2008–2013. J. Microbiol Immunol Infect. 2018. (In press)
Lortholary O, Gangneux J-P, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005–2007). Clin Microbiol Infect. 2011;17:1882–9.
Perkhofer S, Lass-Flörl C, Hell M, Russ G, Krause R, Hönigl M, et al. The Nationwide Austrian *Aspergillus* Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. Int J Antimicrob Agents. 2010;36:531–6.
Li L, Wang J, Zhang W, Yang J, Chen L, Lv S. Risk factors for invasive mold infections following allogeneic hematopoietic stem cell transplantation: a single center study of 190 recipients. Scand J Infect Dis. 2012;44:100–7.
Yan X, Li M, Jiang M, Zou L, Luo F, Jiang Y. Clinical characteristics of 45 patients with invasive pulmonary aspergillosis: retrospective analysis of 1711 lung cancer cases. Cancer. 2009;115:5018–25.
Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. Int J Chron Obstruct Pulmon Dis. 2018;13:1353–64.
Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to tuberculosis. Bull WHO. 2011;89:864–72.
Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med. 2018;6:421–30.
Xu H, Li L, Huang WJ, Wang LX, Li WF, Yuan WF. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China. Clin Microbiol and Infect. 2012;18:403–8.
Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Phil Trans Roy Soc B. 2016;371:20150468.
Chen J, Yang Q, Huang J, Li L. Risk factors for invasive pulmonary aspergillosis and hospital mortality in acute-on-chronic liver failure patients: a retrospective-cohort study. Int J Med Sci. 2013;10:1625–31.
Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 2014;12:145.
Zhang X, Yang M, Hu J, Zhao H, Li L. Epidemiology of invasive pulmonary aspergillosis in patients with liver failure: Clinical presentation, risk factors, and outcomes. J Int Med Res. 2017;46:819–27.
Chronic pulmonary aspergillosis
World Health Organization. Tuberculosis country proviles [cited 2019 Oct 7]. http://www.who.int/tb/country/data/profiles/en/index.html
Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J. 2010;37:865–72.
Denning DW, Pleuvry A, Cole D. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ. 2011;89:864–72.

Invasive aspergillosis
He B, Wan C, Zhou W, Rui Y, Shi Y, Su X. Clinical profile and surgical outcome for different types of chronic pulmonary aspergillosis. Am J Transl Res. 2019;11:3671–79.
Zhan M, Xu B, Zhao L, Li B, Xu L, Sun Q, et al. The serum level of IL-1B correlates with the activity of chronic pulmonary aspergillosis. Can Respir J. 2018;2018:8740491.
Li H, Rui Y, Zhou W, Liu L, He B, Shi Y, et al. Role of the aspergillus-specific IgG and IgM test in the diagnosis and follow-up of chronic pulmonary aspergillosis. Front Microbiol. 2019;10:1438.
Yao Y, Zhou H, Shen Y, Yang Q, Ye J, Fu Y, et al. Evaluation of a quantitative serum *Aspergillus fumigatus*-specific IgM assay for diagnosis of chronic pulmonary aspergillosis. Clin Respir J. 2018;12:2566–72.
Ma X, Wang K, Zhao X, Liu Y, Yu X, Li C et al. Prospective study of the serum *Aspergillus*-specific IgG, IgA and IgM assays for chronic pulmonary aspergillosis diagnosis. BMC Infect Dis. 2019;19:694.
Lee JJ, Chong PY, Lin CB, Hsu AH, Lee CC. High resolution chest CT in patients with pulmonary tuberculosis: characteristic findings before and after antituberculous therapy. Eur J Radiol. 2008;67:100–4.
Smith N, Denning DW. Underlying pulmonary disease frequency in patients with chronic pulmonary aspergillosis. Eur Resp J. 2011;37:865–72.
Allergic bronchopulmonary aspergillosis
Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol. 2013;51:361–70.
To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204.
Lin J, Wang W, Chen P, Zhou X, Wan H, Yin K, et al. Prevalence and risk factors of asthma in mainland China: The CARE study. Respir Med. 2018;137:48–54.
Huang K, Yang T, Xu J, Yang L, Zhao J, Zhang X, et al. China Pulmonary Health (CPH) Study Group. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394:407–18.
Ma YL, Zhang WB, Yu B, Chen YW, Mu S, Cui YL. Prevalence of allergic bronchopulmonary aspergillosis in Chinese patients with bronchial asthma. Zhonghua Jie He He Hu Xi Za Zhi. 2011;34:909–13.
Su N, Lin JT, Wang WY, Chen P, Zhou X, Wan HY, et al. A cross-section study of severe asthma in eight provinces of China. Zhonghua Nei Ke Za Zhi. 2016; 55:917–21.
Guan WJ, Gao YH, Xu G, Lin ZY, Tang Y, Li HM, et al. Aetiology of bronchiectasis in Guangzhou, southern China. Respirology. 2015; 20:739–48.
Severe asthma with fungal sensitization
Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med mycol. 2013;51:361–70.
Zou H, Su L, Fang QH, Ma YM. Correlation between fungal sIgE and bronchial asthma severity. Exp Ther Med. 2013; 6:537–41.
Cryptococcal meningitis
Li Z, Liu Y, Cao H, Huang S, Long M. Epidemiology and clinical characteristics of cryptococcal meningitis in China (1981-2013): a review of the literature. Med Mycol: Open Access. 2017;03.
Chen J, Zhang R, Shen Y, Liu L, Qi T, Wang Z, et al. Serum cryptococcal antigen titre as a diagnostic tool and a predictor of mortality in HIV-infected patients with cryptococcal meningitis. HIV Med. 2018;20:69–73.

Invasive aspergillosis
Guo J, Zhou J, Zhang S, Zhang X, Li J, Sun Y, et al. A case–control study of risk factors for HIV-negative children with cryptococcal meningitis in Shi Jiazhuang, China. BMC Infect Dis. 2012;12:376.
Pneumocystis pneumonia
Chan CK, Alvarez Bognar F, Wong KH, Leung CC, Tan CK, Chan KC, et al. The epidemiology and clinical manifestations of human immunodeficiency virus-associated tuberculosis in Hong Kong. Hong Kong Med J. 2010;16:192–8.
Wang XL, Wei W, An CL. Retrospective study of pneumocystis pneumonia over half a century in mainland China. J Med Microbiol. 2011;60:631–38.
Guo F, Chen Y, Yang SL, Xia H, Li XW, Tong ZH. Pneumocystis pneumonia in HIV-Infected and immunocompromised non-HIV infected patients: a retrospective study of two centers in China. PLoS ONE. 2014; 9:e101943.
Hui M. *Pneumocystis carinii* pneumonia in Hong Kong: a 10 year retrospective study. J Med Microbiol. 2006;55:85–8.
Xiao J, Gao G, Li Y, Zhang W, Tian Y, Huang Y, et al. Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China. PLoS ONE. 2013;8:e75915.
Chan CK, Alvarez Bognar F, Wong KH, Leung CC, Tam CM, Chan KC, et al. The epidemiology and clinical manifestations of human immunodeficiency virus-associated tuberculosis in Hong Kong. Hong Kong Med J. 2010;16:192–8.
Lowe DM, Rangaka MX, Gordon F, James CD, Miller RF. *Pneumocystis jirovecii* pneumonia in tropical and low and middle income countries: a systematic review and meta-regression. PLoS One. 2013;8:369969.
Histoplasmosis
Pan B, Chen M, Pan W, Liao W. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. Mycoses. 2012;56:212–21.
Talaromyces marneffei
Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffei* infection: an emerging disease in mainland China. Mycopathologia. 2012;175:57–67.
Qi T, Zhang R, Shen Y, Liu L, Lowrie D, Song W, et al. Etiology and clinical features of 229 cases of bloodstream infection among chinese HIV/AIDS patients: a retrospective cross-sectional study. Eur J Clin Microbiol Infect Dis. 2016;35:1767–70.
Candidemia
Guo F, Yi Yang Y, Kang Y, Zang B, Cui M, Qin B, et al. Invasive candidiasis in intensive care units in China: a multicenter prospective observational study. J Antimicrob Chemother. 2013;68:1660–8.
Du B, An Y, Kang Y, Yu X, Zhao M, Ma X, et al. China Critical Care Clinical Trial Group. Characteristics of critically ill patients in ICUs in mainland China. Crit Care Med. 2013;41:84–92.
Tan BH, Chakrabarti A, Li RY, Patel AK, Watcharananan SP, Liu Z, et al. Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. Clin Microbiol Infect. 2015;21:946–53.
Montravers P, Mira J-P, Gangneux J-P, Leroy O, Lortholary O. A multicentre study of antifungal strategies and outcome of Candida spp. peritonitis in intensive-care units. Clin Microbiol Infect. 2011;17:1061–7.
Hu S, Tong R, Bo Y, Ming P, Yang H. Fungal peritonitis in peritoneal dialysis: 5-year review from a North China center. Infection. 2018;47:35–43.
Yang ZT, Wu L, Liu XY, Zhou M, Li J, Wu JY, et al. Epidemiology, species distribution and outcome of nosocomial Candida spp. bloodstream infection in Shanghai. BMC Infect Dis. 2014;14:241.

Invasive aspergillosis
Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans Candida spp among candidemia isolates from inpatients in various parts of the world: a systematic review. Int J Infect Dis. 2010;14:e954–66.
Candida peritonitis (CAPD)
Wilkie M, Davies S. Insights on Peritoneal Dialysis in China. Perit Dial Int. 2018;38:S16–8.
Shouci H, Ren t, Yang B, Pei M, Hongtao Y. Fungal peritonitis dialysis: 5-year review from a North China center. Infection. 2019;47:35–43.
Esophageal candidiasis
Smith E, Orholm M. Trends and patterns of opportunistic diseases in Danish AIDS patients 1980–1990. Scand J Infect Dis. 1990;22:665–72.
Choi JH, Lee CG, Lim YJ, Kang HW, Lim CY, Choi JS. Prevalence and risk factors of esophageal candidiasis in healthy individuals: a single center experience in Korea. Yonsei Med J. 2013;54:160–5.
Oral candidiasis
Matee M, Scheutz F, Moshy J. Occurrence of oral lesions in relation to clinical and immunological status among HIV-infected adult Tanzanians. Oral Dis. 2008;6:106–11.
Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Phil Trans Roy Soc B. 2016;371:20150468.
Recurrent vulvovaginal candidiasis
Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R. Global burden of recurrent vulvovaginal candidiasis. Lancet Infect Dis. 2018;18:e339–47.
Fungal keratitis
Song X, Xie L, Tan X, Wang Z, Yang Y, Yuan Y, et al. A multi-center, cross-sectional study on the burden of infectious keratitis in China. PLoS ONE. 2014;9:e113843.
Mucormycosis
Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel). 2019;5:26.
Onychomycosis
Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. J Eur Acad Dermatol Venereol. 2014;28:1480–91.
*Reports published in English during January 1950–October 2019 were searched.

Appendix Table 4. Studies contributing to epidemiology map of talaromycosis in China*

Province	No. cases
Zhejiang Province	
Si Z, Qiao J. *Talaromyces marneffei* infection. N Engl J Med. 2017;377;2580.	1
Yu X, Cai X, Xu X, Zhang L, Huang X, Wang L, et al. Fungemia caused by *penicillium marneffei* in an immunocompetent patient with COPD: a unique case report. Medicine (Baltimore). 2018; 97:e9658.	1
Yu X, Miao K, Zhou C, Cai Y, Huang X, Chen Y, et al. *T. Marneffei* infection complications in an HIV-negative patient with pre-existing pulmonary sarcoidosis: a rare case report. BMC Infect Dis. 2018;18;390.	1
Wang P, Chen Y, Xu H, Ding L, WuZ, Xu Z. Acute disseminated *Talaromyces marneffei* in an immunocompetent patient. Mycopathologia. 2017;182; 751–4.	1
Huang SS, Zhang SN, Ye JR, Su SS, Lin PC, Li YP, et al. Diagnostic performance of pathology, culture and ROSE of lung biopsy for suspected pulmonary infectious diseases. 2019;99:3340–4.	3
Ge Y, Xu Z, Hu Y, Huang M. Successful voriconazole treatment of *Talaromyces marneffei* infection in an HIV-negative patient with osteolytic lesions. J Infect Chemother. 2019;25:204–7.	1
Su SS, Zhang SN, Ye JR, Xu LN, Lin PC, Xu HY, et al. Disseminated *Talaromyces marneffe*i and *Mycobacterium avium* infection accompanied Sweet's syndrome in a patient with anti-interferon-γ. Infect Drug Resist. 2019;12:3189–95.	1
Cui Y, Jin C, Li X, Wu N. *Penicillium marneffei* infection presenting as vulv-ulcer in an HIV-infected woman. Eur J Med Res. 2011;16:426–6.	1
Xia XJ, Shen H, Xu AE. Cutaneous *Penicillium marneffei* infection in a patient with idiopathic CD4(+) lymphocytopenia. J Dermatol. 2015;42:812–4.	1
Hong Kong	
Wong SCY, Sridhar S, Ngan AHY, Chen JHK, Poon RWS, Lau SKP, et al. Fatal *Talaromyces marneffei* infection in a patient with autoimmune hepatitis. Mycopathologia. 2018;183:615–8.	1
Hung HG, Lok KH. Intestinal *Penicillium marneffei*: an unusual cause of chronic diarrhea in an AIDS patient. J Dig Dis. 2010;11:189–91.	1
Chan YH, Wong KM, Lee KC, Kwok PC, Chak WL, Choi KS, et al. Pneumonia and mesenteric lymphadenopathy caused by disseminated *Penicillium marneffei* infection in a cadaveric renal transplant recipient. Transpl Infect Dis. 2004;6:28–32.	1
Lee PP, Lao-Araya M, Yang J, Chan KW, Ma H, Pei LC, et al. Application of flow cytometry in the diagnostics pipeline of primary immunodeficiencies underlying disseminated *Talaromyces marneffei* infection in HIV-negative children. Front Immunol. 2019;10:2189.	8
Wong KH, Lee SS. Comparing the first and second hundred AIDS cases in Hong Kong. Singapore Med J. 1998;39:236–40.	19
Wu TC, Chan JW, Ng CK, Tsang DN, Lee MP, Li PC. Clinical presentations and outcomes of *Penicillium marneffei* infections: a series from 1994 to 2004. Hong Kong Med J. 2008;14:103–9.	47
Ma BH, Ng CS, Lam R, Wan S, Wan IY, Lee TW, et al. Recurrent hemoptysis with *Penicillium marneffei* and *Stenotrophomonas maltophilia* in Job's syndrome. Can Respir J. 2009;16:e50–2.	1

Province	No. cases
Wong SS, Woo PC, Yuen KY. *Candida tropicalis* and *Penicillium marneffei* mixed fungaemia in a patient with Waldenström's macroglobulinaemia. Eur J Clin Mircobiol Infect Dis. 2001;20:132–5.	1
Guangdong Province	
Lu S, Li X, Calderone R, Zhang J, Ma J, Cai W, et al. Whole blood nested PCR and real-time PCR amplification of *Talaromyces marneffei* specific DNA for diagnosis. Med Mycol. 2016;54:162–8.	23
Lei M, Yu U, Zhang N, Deng J. An HIV-negative infant with systemic *Talaromyces marneffei* infection. Int J Infect Dis. 2018;77:3–4.	1
Chi XH, Xue YM, Wang QS, Li GP, Zhou HS, Qi YS. Diagnosis and treatment of diffusible *Penicillium marneffei* in human immunodeficiency virus-negative patients: a challenge for the physician. Indian J Med Microbiol. 2017;35:617–9.	1
Li HR, Xu NL, Lin M, Hu XL, Chen JH, Chen YS, et al. Diffuse interstitial and multiple cavitary lung lesions due to *Talaromyces marneffei* infection in a non-HIV patient. New Microbes New Infect. 2015;8:14–6.	1
Li LH, Hu FY, Chen WS, Cai WP, Song WN, Kuang YL, et al. Genetic diversity analysis of *Penicillium marneffei* isolated from AIDS patients in Guangdong, China using randomly amplified polymorphic DNA. Chin Med J (Engl). 2012;125:823–7.	163
Zhou F, Bi X, Zou X, Xu Z, Zhang T. Retrospective analysis of 15 cases of *Penicilliosis marneffei* in a southern China hospital. Mycopathologia. 2014;177:271–9.	15
Zhang J, Huang X, Zhang X, Zhu Y, Liao K, Ma J. Coinfection of disseminated *Talaromyces marneffei* and *Mycobacteria kansasii* in a patient with papillary thyroid cancer: a case report. Medicine (Baltimore). 2017;96:e9072.	1
Wang YF, Xu HF, Han ZG, Zeng L, Liang CY, Chen YJ. Serological surveillance for *Penicillium marneffei* infection in HIV-infected patients during 2004–2011 in Guangzhou, China. Clin Microbiol Infect. 2015;21:484–9.	761
Lau SKP, Xing F, Tsang CC, Tang JYM, Tan YP, Ye H, et al. Clinical characteristics, rapid identification, molecular epidemiology and antifungal susceptibilities of *Talaromyces marneffei* infections in Shenzhen, China. Mycoses. 2019;62:450–7.	7
Fan H, Huang L, Yang D, Lin Y, Lu G, Xie Y, et al. Pediatric hyperimmunoglobulin E syndrome: a case series of 4 children in China. Medicine (Baltimore). 2018;97:e0215.	1
Luo DQ, Chen MC, Liu JH, Li Z, Li HT. Disseminated *Penicillium marneffei* infection in an SLE patient: a case report and literature review. Mycopathologia. 2011;171:191–6.	1
Peng J, Chen Z, Cai R, Huang X, Lin L, Liang W, et al. Recovery from *Talaromyces marneffei* involving the kidney in a renal transplant recipient: a case report and literature review. Transpl Infect Dis. 2017;19.	1
Liyan X, Changming L, Xianyi Z, Luxia W, Suisheng X. Fifteen cases of penicilliosis in Guangdong, China. Mycopathologia. 2004;158:151–5.	15
Xian J, Hunag X, Li Q, Peng X, Peng X. Dermatoscopy for the rapid diagnosis of *Talaromyces marneffei* infection: a case report. BMC Infect Dis. 2019;19:707.	1
Lao M, Zhan Z, Su F, Li H, Yang Z, Chen H, et al. Invasive mycoses in patients with connective tissue disease from Southern China: clinical features and associated factors. Arthritis Res Ther. 2019; 21:71.	2
Lu PX, Zhu WK, Liu Y, Chen XC, Zhan NY, Liu JQ, et al. Acquired immunodeficiency syndrome associated with disseminated *Penicillium marneffei* infection: report of 8 cases. Chin Med J (Engl). 2005; 118:1395–9.	8

Province	No. cases
Ye F, Luo Q, Zhou Y, Xie J, Zeng Q, Chen G, et al. Disseminated *Penicilliosis marneffei* in immunocompetent patients: a report of two cases. Indian J Med Microbiol. 2015;33:161–5.	2
Du Q, Tong Ck. *Talaromyces (Penicillium) marneffei* infection. IDCases. 2018;13:e00428.	1
Li Q, Wang C, Zeng K, Peng X,Wang F. AIDS-associated disseminated *talaromycosis (penicilliosis) marneffei.*J Dtsch Dermatol Ges. 2018;16:1256–9.	1
Beijing	
Liu X, Wu H, Huang X. Disseminated *Penicillium marneffei* infection with IRIS. IDCases. 2015; 2:92–3.	1
Li H, Sang J, Li R, Liu Y, Zhang J. Disseminated *Penicillium Marneffei* infection with verrucoid lesions in an AIDS patient in Beijing, a non-endemic region. Eur J Dermatol. 2010;20:378–80.	1
Lu ZH, Liu HR, Xie XL, Wang AX, Liu TH. Infection of *Penicillium marneffe.* Zhonghua Bing Li Xue Za Zhi. 2004;33:53640.	1
Xiao J, Gao G, Li Y, Zhang W, Tian Y, Huang Y, et al. Spectrums of opportunistic infections and malignancies in HIV-infected patients in tertiary care hospital, China. PLoS One. 2013;8:e75971.	11
Zhao DW, Zhang T, Ma DQ, Wang W, Yuan CW, Duan Y. Disseminated *Penicillium marneffei* infection in acquired immunodeficiency syndrome: a case report. Chin Med J (Engl), 2005;118:1054–6.	1
Qu H, Song Y, Li R, Yu J. Image gallery: an unusual cutaneous presentation of disseminated *penicilliosis marneffei* in an immunocompetent patient. Br J Dermatol. 2017;177:e67.	1
Jiang X, Zhou D. Diagnosis of *Penicillium marneffei* infection from a blood film. Br J Haematol. 2015;171:670.	1
Guangxi Province	
Liu GN, Huang JS, Zhong NX, Zhang JQ, Zou ZX, Yang ML, et al. *Penicillium marneffei* infection within an osteolytic lesion in an HIV-negative patient. Int J Infect Dis. 2014;23:1–3.	1
Li X, ZhengY, Wu F, Mo D, Liang G, Yan R, et al. Evaluation of quantitative real-time PCR and Platelia galactomannan assays for the diagnosis of disseminated *Talaromyces marneffei* infection. Med Mycol. 2019 May 27. Pii:myz052.	36
Qiu Y, Zeng W, Zhang H, Zhang X, Tang S, Zhang J. Comparison of pleural effusion features and biomarkers between talaromycosis and tuberculosis in non-human immunodeficiency virus-infected patients. BMC Infect Dis. 2019;19:745.	19
Deng Z, Ribas JL, Gibson DW, Connor DH. Infections caused by *Penicillium marneffei* in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. Rev Infect Dis. 1988;10:640–52.	4
Deng Z, Liu x. Disseminated *Penicilliosis marneffei* in a patient with acquired immunodeficiency syndrome: a first case report from China. Chin Med J (Engl). 2000;113:1049–50.	1
Jiang J, Meng S, Huang S, Ruan Y, Lu X, Li JZ, et al. Effects of *Talaromyces marneffei* infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. Clin Microbiol Infect. 2019;25:233–41.	1093
Ouyang Y, Cai S, Liang H, Cao C. Administration of voriconazole in disseminated *Talaromyces (Penicillium) Marneffei* infection: a retrospective study. Mycopathologia. 2017;182:569–75.	112
Shi N, Kong J, Wang K, Cao C. Coinfection with *Talaromyces marneffei* and other pathogens associated with acquired immunodeficiency. JAMA Dermatol. 2019 Jul 24.	1

Province	No. cases
Xu H, Liu D, He X, Zheng D, Deng Y. Sweet's syndrome associated with *Talaromyces marneffei* and *Mycobacterium abscessus* infection due to anti-interferon-gamma autoantibodies. Indian J Dermatol. 2018;63:428–30.	1
Han J, Lun WH, Meng ZH, Huang K, Mao Y, Zhu W, et al. Mucocutaneous manifestations of HIV-infected patients in the era of HAART in Guangxi Zhuang Autonomous Region, China. J Eur Acad Dermatol Venereol. 2013;27:376–82.	40
Guo J, Li BK, Li TM, Wei FL, Fu YJ, Zheng YQ, et al. Characteristics and prognosis of *Talaromyces marneffei* infection in non-HIV-infected children in southern China. Mycopathologia. 2019 Aug 31.	11
Qiu Y, Zhang J, Liu G, Zhong X, Deng J, He Z, et al. Retrospective analysis of 14 cases of disseminated *Penicillium marneffei* infection with osteolytic lesions. BMC Infect Dis. 2015;15:47.	14
Lin F, Qiu Y, Zeng W, Liang Y, Zhang J. *Talaromyces marneffei* infection in a lung cancer patient: a rare case report. BMC Infect Dis. 2019;19:336.	1
Zeng W, Qiu Y, Lu D, Zhang J, Zhong X, Liu G. A retrospective analysis of 7 human immunodeficiency virus-negative infants infected by *Penicillium marneffei*. Medicine (Baltimore). 2015;94:e1439.	7
Qiu Y, Liao H, Zhang J, Zhong X, Tan C, Lu D. Differences in clinical characteristics and prognosis of penicilliosis among HIV-negative patients with or without underlying disease in southern China: a retrospective study. BMC Infect Dis. 2015;15:525.	109
Qiu Y, Pan M, Zhang J, Zhong X, Li Y, Zhang H, et al. Two unusual cases of human immunodeficiency virus-negative patients with *Talaromyces marneffei* infection. Am J Trop med Hyg. 2016;95:426–30.	2
Qin L, Zhao L, Tan C, Chen XU, Yang Z, Mo W. A novel method of combining periodic acid Schiff staining with Wright-Giemsa staining to identify the pathogens *Penicillium marneffei*, *Histoplasma capsulatum*, *Mucor* and *Leishmania donovani* in bone marrow smears. Exp Ther Med. 2015;9:1950–4.	25
Li JS, Pan LQ, Wu SX, Su SX, Su SB, Shan LY. Disseminated *penicilliosis marneffei* in China. Report of three cases. Chin Med J (Engl). 1991;104:247–51.	3
Zeng W, Qiu Y, Tang S, Zhang J, Pan M, Zhong X. Characterization of anti-interferon-γ antibodies in HIV-negative patients infected with disseminated *Talaromyces marneffei* and cryptococcosis. Open Forum Infect Dis. 2019;6:ofz208.	20
Qiu Y, Zhang JQ, Pan ML, Zeng W, Tang SD, Tan CM. Determinants of prognosis in *Talaromyces marneffei* infections with respiratory system lesions. Chin Med J (Engl). 2019;132:1909–18.	126
Qiu Y, Zhang J. Behcet's disease with pulmonary artery aneurysm and *Talaromyces marneffei*. Int J Infect Dis. 2017;54:34–5.	1
Qiu Y, Lu D, Zhang J, Zhong X, Liu G, Li B. Treatment of disseminated *Talaromyces marneffei* with tracheal infection: two case reports. Mycopathologia. 2015;180:245–9.	2
Mo W, Deng Z, Li S. Clinical blood routine and bone marrow smear manifestations of disseminated *Penicilliosis marneffei*. Chin Med J (Engl). 2002;115:1892–4.	13
Li Y, Lin Z, Shi X, Mo L, Li W, Mo W, et al. Retrospective analysis of 15 cases of *Penicillium marneffei* infection in HIV-positive and HIV-negative patients. Microb Pathog. 2017;105:321–5.	15
Wei XG. Report of the first case of *penicilliosis marneffei* in China. Zhonghua Yi Xue Za Zhi. 1985; 65:533–4.	1

Province	No. cases
Qiu Y, Tang Y, Zhang J, Yi X, Zhong X, Liu G, Xu H, et al. A retrospective analysis of seven patients with acquired immunodeficiency syndrome and pharyngeal and/or laryngeal *Talaromyces marneffei* infection. Clin Otolaryngol. 2017;42:1061–6.	7
Nong S, Liang J. Bone marrow *Penicillium marneffei* infection in acquired immunodeficiency syndrome patients: report of 35 cases. Trop Biomed. 2013;30:89–91.	35
Shanghai	
Qi T, Zhang R, Shen Y, Liu L, Lowrie D, Song W, et al. Etiology and clinical features of 229 cases of bloodstream infection among Chinese HIV/AIDS patients: a retrospective cross-sectional study. Eur J Clin Microbiol Infect Dis. 2016;35:1767–70.	43
Chen J, Zhang R, Shen Y, Liu L, Qi T, Wang Z, et al. Clinical characteristics and prognosis of penicilliosis among human immunodeficiency virus-infected patients in eastern China. Am J Trop Med Hyg. 2017;96:1350–4.	48
Chen M, Houbraken J, Pan W, Zhang C, Peng H, Wu L, et al. Pulmonary fungus ball caused by *Penicillium capsulatum* in a patient with type 2 diabetes: a case report. BMC Infect Dis. 2013;13:496.	2
Zhang HC, Zhang QR, Ai JW, Cui P, Wu HL, Zhang WH, et al. The role of bone marrow metagenomics next-generation sequencing to differential diagnosis among visceral leishmaniasis, histoplasmosis, and *talaromycosis marneffei*. Int J lab Hematol. 2019 Oct 8.	1
Zhu YM, Ai JW, Xu B, Cui P, Cheng Q, Wu H, et al. Rapid and precise diagnosis of disseminated *T. marneffei* infection assisted by high-throughput sequencing of multifarious specimens in a HIV-negative patient: a case report. BMC Infect Dis. 2018;18:379.	1
Zhu LP, Yang FF, Weng XH, Huang YX, Chen S, Shi GF, et al. Hepatic safety of itraconazole intravenous solution in treatment of invasive fungal infection. Zhonghua Yi Xue Za Zhi. 2006; 86:2028–32.	1
Shen YZ, Wang ZY, Lu HZ. *Penicillium marneffei* chylous ascites in acquired immune deficiency syndrome: a case report. World J Gastronterol. 2012;18:5312–4.	1
Fujian Province	
Li HR, Cai SX, Chen YS, Yu ME, Xu NL, Xie BS, et al. Comparison of *Talaromyces marneffei* infection in human immunodeficiency virus-positive and human immunodeficiency virus-negative patients from Fujian, China. Chin Med J (Engl). 2016;129:1059–65.	26
Lai JL, Chen YH, Liu YM, Yuan JJ, Lin J, Huang AQ, et al. Prevalence and risk factors of anaemia in hospitalised HIV-infected patients in southeast China: a retrospective study. Epidemiol Infect. 2019; 147:e81.	61
Chen Y, Huang A, Ao W, Wang Z, Yuan J, Song Q, et al. Proteomic analysis of serum proteins from HIV/AIDS patients with *Talaromyces marneffei* infection by TMT labeling-based quantitative proteomics. Clin Proteomics. 2018;15:40.	18
Wang YG, Cheng JM, Ding HB, Lin X, Chen GH, Zhou M, et al. Study on the clinical features and prognosis of *Penicilliosis marneffei* without human immunodeficiency virus infection. Mycopathologia. 2018;183:551–8.	6
Hubei Province	
Han P, Yan W, Luo Y, Tu W, He JY, Liu JM, et al. Chronic bronchitis with fungal infection presenting with marked elevation of serum carbohydrate antigen 19-9: a case report. Int J Clin Exp Pathol. 2014;7:6307–12.	1

Province	No. cases
Liu XY, Chen KL, You Y, Chen WX, Zou P. The differential features of bone marrow morphology of several rare infectious disorders. Zhoughua Nei Ke Za Zhi. 2005;44:902–5.	1
Xiang Y, Guo W, Liang K. An unusual appearing skin lesion from *Penicillium marneffei* infection in an AIDS patient in central China. Am J Trop Med Hyg. 2015;93:3.	1
Sichuan Province	
Pang W, Shang P, Li Q, Xu J, Bi L, Zhong J, et al. Prevalence of opportunistic infections and causes of death among hospitalized HIV-infected patients in Sichuan, China. Tohoku J Exp Med. 2018; 244:231–42.	3
Liao X, Ran Y, Chen H, Meng W, Xiang B, Kang M, et al. Disseminated *Penicillium marneffei* infection associated with AIDS, report of a case. Zhonghua Yi Xue Za Zhi. 2002;82:326–9.	1
Xu X, Ran X, Pradhan S, Lei S, Ran Y. Dermoscopic manifestations of *Talaromyces (Penicillium) marneffei* infection in an AIDS patient. Indian J Dermatol Venereol Leprol. 2019;85:348.	1
Zhiyong Z, Mei K, Yanbin L. Disseminated *Penicillium marneffei* infection with fungemia and endobronchial disease in an AIDS patient in China. Med Princ Pract. 2006;15:235–7.	1
Hunan Province	
Zhang Z, Tao F, Li Y, Xiao Y, Zhang Z, Liu J. Disseminated *Penicillium marneffei* infection recurrence in a non-acquired immune deficiency syndrome patient: a case report. Mol Clin Oncol. 2016;4:829–31.	1
Liu D, Zhong LL, Li Y, Chen M. Recurrent fever, hepatosplenomegaly and eosinophilia in a boy. Zhongguo Dang Dai Er Ke Za Zhi. 2016;18:1145–9.	1
Yunnan Province	
Li YY, Saeed U, Wei SS, Wang L, Kuang YQ. Both coinfections of *Penicillium marneffei* and *Cryptococcus neoformans* in AIDS patient: a report of rare case. AIDS. 2017;31:2171–2.	1
Taiwan	
Yen YF, Chen M, Jen I, Lan YC, Chuang PH, Liu YL, et al. Association of HIV and opportunistic infections with incident stroke: a nationwide population-based cohort study in Taiwan. J Acquir Immune Defic Syndr. 2017;74:117–25.	126
Cheng NC, Wong WW, Fung CP, Liu CY. Unusual pulmonary manifestations of disseminated *Penicillium marneffei* infection in three AIDS patients. Med Mycol. 1998;36:429–32.	3
Chang cc, Liao ST, Huang WS, Liu JD, Shih LS. Disseminated *Penicillium marneffei* infection in a patient with acquired immunodeficiency syndrome. J Formos Med Assoc. 1995;94:527–35.	1

*We searched the PubMed database for articles published in China during January 1, 1950–October 7, 2019, using ‘‘*penicillium marneffeii*,” ‘‘talaromycosis,’’ or ‘‘penicilliosis’’ as the search strings for talaromycosis.

Appendix Table 5. Studies contributing to epidemiology map of histoplasmosis in China*

Province	No. cases
Hunan Province	
Zhang Y, Su X, Li Y, He R, Hu C, Pan P. Clinical comparative analysis for pulmonary histoplasmosis and progressive disseminated histoplasmosis. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2016;41:1345–51.	12
Zhou L, Fan S, Liang Q, Peng Y, Zong D, Ouyang R. Clinical characteristics of histoplamosis in 8 patients: case report and literature review. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2016;41:644–52.	8
Zhao B, Xia X, Yin J, Zhang X, Wu E, Shi Y, et al. ,Epidemiological investigation of *Histoplasma capsulatum* infection in China. Chin Med J (Engl). 2001;114:743–6.	47
Zhu C, Wang G, Chen Q, He B, Wang L. Pulmonary histoplasmosis in a immunocompetent patient: a case report and literature review. Ex Ther Med. 2016;12:3256–60.	1
Clinical features and endemic trend of histoplasmosis in China: a retrospective analysis and literature review. Clin Respir J. 2019; Dec 07.	34
Sichuan Province	
Zhu LL, Wang J, Wang ZJ, Wang Yp, Yang JL. Intestinal histoplasmosis in immunocompetent adults. World J Gastroenterol. 2016;22:4027–33.	1
Yang B, Lu L, Li D, Liu L, Huang L, Chen L, et al. Colonic involvement in disseminated histoplasmosis of an immunocompetent adult: case report and literature review. BMC Infect Dis, 2013;13:143.	1
Wen FQ, Sun YD, Watanabe K, Yoshida M, Wu JN, Baum GL. Prevalence of histoplasmin sensitivity in healthy adults and tuberculosis patients in southwest China. J Med Vet Mycol. 1996;34:1714.	67
Xiong XF, Fan LL, Kang M, Wei J, Cheng DY. Disseminated histoplasmosis: a rare clinical phenotype with difficult diagnosis. Respirol Case Rep. 2017; 5:e00220.	1
Beijing	
Gong P, Cao Z, Mu X, Dong X, Wang K, Feng R, et al. The clinical-radiologic-pathologic features of imported pulmonary histoplasmosis. Zhonghua Jie He He Hu Xi Za Zhi, 2015;38:23–8.	3
Zhao CS, Zhao SY, Liu G, Xi-Wei X. Risk factors of invasive fungal infections in patients admitted to non-hematological oncology department and pediatric intensive care unit. Zhonghua Er Ke Za Zhi. 2013;51:589–601.	1
Zhejiang Province	
Liu B, Qu L, Zhu J, Yang Z, Yan S. Histoplasmosis mimicking metastatic spinal tumour. J Int med Res. 2017;45:1440–6.	1
Shen G, Chai Y, Zhang GF, Wei HQ, Yue L. Diagnosis and treatment of pulmonary histoplasmoma: report of 3 cases. Zhonghua Yi Xue Za Zhi. 2007;87:760–2.	3
Ye C, Zhang G, Wang J, Chai Y. Histoplasmosis presenting with solitary pulmonary nodule: two cases mimicking pulmonary metastases. Niger J Clin Pract. 2015;18:304–6.	2
Zhang X, Jin J, Cai C, Zheng R, Wang Y, Xu Y. Amphotericin B liposome-induced acrocyanosis and elevated serum creatinine. Indian J Pharmacol. 2016;48:321–3.	1
Huang L, Wu Y, Miao X. Localized *Histoplasma capsulatum* osteomyelitis of the fibula in an immunocompetent teenage boy: a case report. BMC Infect Dis. 2013;13:132.	1

Province	No. cases
Shanghai	
Wang Y, Pan B, Wu J, Bi X, Liao W, Pan W, et al. Detection and phylogenetic characterization of a case of *Histoplasma capsulatum* infection in mainland China. Am J Trop med Hyg. 2014;80:1180–3.	1
Zhang HC, Zhang QR, Ai JW, Cui P, Wu HL, Zhang WH, et al. The role of bone marrow metagenomics next-generation sequencing to differential diagnosis among visceral leishmaniasis, histoplasmosis, and *talaromycosis marneffei*. Int J lab Hematol. 2019 Oct 8.	1
Guangxi Province	
Qin L, Zhao L, Tan C, Chen XU, Yang Z, Mo W. A novel method of combining periodic acid Schiff staining with Wright-Giemsa staining to identify the pathogens *Penicillium marneffei*, *Histoplasma capsulatum*, *Mucor* and *Leishmania donovani* in bone marrow smears. Exp Ther Med. 2015;9:1950–4.	10
Li ZS. Histoplasmosis in south Guangxi (report of 5 cases). Zhonghua Yi Xue Za Zhi. 1982;62:267–9.	5
Cao C, Bulmer G, Li J, Liang L, Lin Y, Xu Y, et al. Indigenous case of disseminated histoplasmosis from the *Penicillium marneffei* endemic area of China. Mycopathologia. 2010;170:4750.	1
Jiangsu Province	
Zhao B, Xia X, Yin J, Zhang X, Wu E, Shi Y. Epidemiological investigation of *Histoplasma capsulatum* infection in China. Chin Med J (Engl). 2001;114:743–6.	80
Lü PH, Zhao BL, Shi Y, Wen YT. The diagnostic value of detecting plasma 1,3-beta-D-glucan for invasive fungal infections. Zhonghua Jie He He Hu Xi Za Zhi, 2007;30:31–4.	1
Zhao B, Yin J, Xia X. Investigation on the epidemiology of *Histoplasma capsulatum* infection in Nanjing district. Zhonghua Liu Xing Bing Xue Za Zhi. 1998;19:215–7.	49
Xinjiang Province	
Zhao B, Xia X, Yin J, Zhang X, Wu E, Shi Y, et al. Epidemiological investigation of *Histoplasma capsulatum* infection in China. Chin Med J (Engl). 2001;114:743–6.	11
Taiwan	
Liu JW, Huang TC, Lu YC, Liu HT, Li CC, Wu JJ, et al. Acute disseminated histoplasmosis complicated with hypercalcaemia. J Infect. 1999;39:88–90.	1
Tseng TC, Liaw SJ, Hsiao CH, Wang CY, Lee LN, Huang TS, et al. Molecular evidence of recurrent histoplasmosis with 9-year latency in a patient with Addison's disease. J Clin Microbiol. 2005; 43:4911–3.	1
Chang YG, Chen PJ, Hung CC, Chen MY, Lai mY, Chen DS. Opportunistic hepatic infections in AIDS patients with fever of unknown origin. J Formos Med Assoc. 1999;98:5–10.	1
Lai CH, Huang CK, Chin C, Yang YT, Lin HF, Lin HH. Indigenous case of disseminated histoplasmosis, Taiwan. Emerg Infect Dis. 2007;13:127–9.	1
Chang YT, Huang SC, Hu SY, Tsan YT, Wang LM, Wang RC. Disseminated histoplasmosis presenting as haemolytic anaemia. Postgrad Med J. 2010;86:443–4.	1
Chongqing Province	
Ge L, Zhou C, Song Z, Zhang Y, Wang L, Zhng B, et al. Primary localized histoplasmosis with lesions restricted to the mouth in a Chinese HIV-negative patient. Int j Infect Dis. 2010;14 Suppl 3:e325–8.	1
Guangdong Province	

Province	No. cases
Ai XB, Wang ZJ, Dong QC, Lin X, Chen YP, Gong FY. Ileum histoplasmosis mimicking intestinal tuberculosis and Crohn's disease. Case Rep Gastroenterol. 2018;12:63–8.	1
Huang LF, Tang XP, Cai WP, Chen XJ, Lei CJ, Li LH, et al. An analysis of opportunistic infection in 762 inpatients with human immunodeficiency virus infection in Guangdong areas. Zhonghua Nei Ke Za Zhi, 2010;49:653–6.	1
Meng Y, Cai S, Li X. Pathologically confirmed histoplasmosis: analysis of 14 cases. Nan Fang Yi Ke Da Xue Xue Bao. 2013;33;296–8.	14
Dang Y, Jiang L, Zhang J, Pan B, Zhu G, Zhu F, et al. Disseminated histoplasmosis in an immunocompetent individual diagnosed with gastrointestinal endoscopy: a case report. BMC Infect Dis. 2019;19:992.	1
Hubei Province	
Han P, Yan W, Luo Y, Tu W, He JY, Liu JM, et al. Chronic bronchitis with fungal infection presenting with marked elevation of serum carbohydrate antigen 19-9: a case report. Int J Clin Exp Pathol. 2014; 7:6307–12.	1
Liu XY, Chen KL, You Y, Chen WX, Zou P. The differential features of bone marrow morphology of several rare infectious disorders. Zhonghua Nei Ke Za Zhi. 2005;44:902–5.	7
Li X, Li J, Feng GQ, Gui XE, Zeng XC. A primary investigation on disseminated histoplasmosis in Hubei. Zhonghua Liu Xing Bing XUe Za Zhi. 2003;24:708–10.	1
Hong Kong	
Wong KF, Cheng NH. Fever and productive cough in a patient with AIDS. Clin Infect Dis. 2011; 52:646–7.	1
Tsui WM, Ma KF, Tsang DN. Disseminated *Penicillium marneffei* infection in HIV-infected subject. Histopathology. 1992;20:287–93.	4

* We searched the PubMed database for articles published in China during January 1, 1950–October 7, 2019, using “histoplasmosis” or “*Histoplasma*” for histoplasmosis.